R E M A R K S

Claims 246- 252, 255, 264-267, 271-275 are pending in the above-referenced application. Claims 249 and 250 have been amended to correct dependencies. As will be discussed below, claims 246, 247, 248, 252, 255, 264, 265, 267, and 271-274 have been amended to more distinctly claim that which Applicants regard as their invention and will be discussed in further detail below. Claim 275 has been added to recite a specific embodiment. No new matter has been added. Therefore, the claim amendments and new claim 275 are supported by the specification.

An additional several part Restriction Requirement has been issued. Applicants respectfully traverse the Restriction Requirement in its entirety. However, Applicants have as requested made the requisite elections. For ease of organization, each part of the Restriction Requirement is discussed separately below.

I. The type of modified element in the construct, which may be 1) a modified nucleotide, 2) a nucleotide analog, or 3) a combination of both (claim 246, 267, 271, and 273 among others)

A. Election: Modified nucleotide.

B. Claims readable on Election-claims 246, 255, 271, 273, 274 and 275

Before discussing reasons for traversal, Applicants note that claims 246, 255, 271, 273 and 274 have been amended to delete the phrase “or a combination of the foregoing”. Claim 255 has been amended to remove reference to “nucleotide analog or analogs”.

C. Traversal

Applicants traverse for several reasons. First, as Examiner states in the Restriction Requirement:

> Related inventions are distinct if (1) the inventions as claimed are either not capable of use together or can have a

> materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j).

In this particular Restriction Requirement, "modified nucleotides" and "nucleotide analog or analogs" actually do overlap in scope. Specifically, modified nucleotides are actually nucleotide analogs. Applicants do concede that there may be some nucleotide analogs such as inosine which would not be deemed to be modified unless the inosine itself is modified in Froehler. However, modified nucleotides are always nucleotide analogs. Examples are phosphoramidates and methyl phosphonates (see, eg., Froehler et al., Nucleic Acids Res. 16: 4831, attached hereto as Exhibit 1). Nucleotides with phosphoramidate and methylphosphonate linkages are referred to as "analogs". Moreover, these nucleotides are also "modified nucleotides". Applicants also note that modified nucleotides and nucleotide analogs can certainly be used together.

Applicants further note that *contra* to assertions made in the Restriction Requirement, it would not be a serious burden to search "modified nucleotides" and "nucleotide analogs", especially given the overlapping nature of the subject matter. Modified nucleotides and nucleotide analogs should not have different classifications and should not require a different field of search. Clearly, prior art applicable to "modified nucleotides" should be applicable to "nucleotide analogs". *Contra* to assertions made in the Restriction Requirement, significantly different considerations of the patent and non-patent literature would need to be made.

II. Whether the construct comprises 1) at least one modified nucleotide with a fusogenic protein and at least one modified nucleotide with a ligand; 2) at least one nucleotide analog with a fusogenic protein and at least one nucleotide analog with a ligand; 3) at least one modified nucleotide with a fusogenic protein and at least one nucleotide analog with a ligand; or 4) at least one nucleotide analog with a fusogenic protein and at least one modified nucleotide with a ligand (claim 246)

A. Election: at least one modified nucleotide with a fusogenic protein and at least one modified nucleotide with a ligand.

B. Claims readable on Election-claim 246. As noted above, claim 246 has been amended to delete the phrase "or a combination of the foregoing".

C. Reasons for traversal

Again, the inventions are not distinct, since specific groups recited overlap in scope with one another. As noted above, modified nucleotides are actually nucleotide analogs.

Further, as noted above, given the nature of the overlapping subject matter, it would not be an undue burden to search all of the different groups recited. Modified nucleotides and nucleotide analogs should not have different classifications and should not require a different field of search.

III. The type of nucleic acid product generated from the construct, which may be 1) an antisense RNA; 2) antisense DNA; 3) sense RNA; 4) ribozymes; 5) messenger RNA; or 6) a combination of any of the foregoing (claim 246, 271, and 273)

A. Election-RNA.

B. Claims readable on the Election: Claims 246, 271 and 273. Applicants note that claims 246, 271 and 273 have been amended to recite that the nucleic acid product is RNA.

C. Reasons for Traversal

Applicants traverse the Restriction Requirement because it would not be an undue burden to search the groups and the recited groups are not independent and distinct. However, to advance prosecution, claims 246, 271 and 273 have been amended to recite that the nucleic acid product is an RNA nucleic acid product.

The inventions in this particular grouping are not distinct for a number of reasons. The invention is directed to the construct itself, not the product produced. Specifically, the product produced is not necessarily dependent on the construct itself but on other factors such as type of polymerase used.

IV. Whether 1) the construct or 2) a portion of the construct is 1) linear; 2) circular; or 3) branched (claim 247)

A. Election-At least a portion of the construct is circular.

B. Claims readable on the Election: 247, 273. Applicants note that claims 247 has been amended to recite that at least a portion of the construct is circular, linear or branched.

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 247 just recites three groups.

Claim 247 has been amended to recite "at least a portion of the construct is…". Therefore, it is possible that a construct could contain circular, linear and/or branched regions and could be used together. The claimed construct whether in circular, linear or branched form would have a similar function. Given that the construct could contain both groups, the recited groups are not mutually exclusive and they overlap in scope. It is Applicants' view that these groups should not have different classifications and should not require a different field of search.

Furthermore, in Applicants' view, the functionality of the construct would not be significantly different in view of whether a portion is linear, circular or branched. Thus the inventions are not distinct.

V. Whether 1) the construct or 2) a portion of the construct is 1) single stranded; 2) double stranded; 3) partially double stranded; or 4) triple stranded (claims 248 and 249)

A. Election-At least a portion of the construct is double-stranded.

B. Claims readable on the Election: 248 and 249. Applicants note that

claims 248 has been amended to recite that at least a portion of the construct is single-stranded, double-stranded or triple-stranded.

C. Reasons for Traversal

In Applicants' view, it would not be an undue burden to search the groups. Applicants note that only three groups are recited.

It is additionally Applicants position that the groups recited are indeed not distinct. As noted above, claim 248 has been amended to recite "at least a portion of the construct is…". Therefore, it is possible that a construct could contain single-stranded, double-stranded and/or triple-stranded regions and could be used together. The claimed construct whether single-stranded, double-stranded or triple-stranded would have a similar function, template synthesis for a biological product having biological activity. Further, it is Applicants view that these groups should not have different classifications and should not require a different field of search.

VI. Whether the construct comprises 1) DNA; 2) RNA; 3) a DNA-RNA hybrid; 4) a DNA-RNA chimera; or 4) a combination of any of the foregoing (claim 252)

A. Election-The construct comprises DNA.

B. Claims readable on the Election: 252. Applicants note that claims 252 has been amended to recite that the construct comprises DNA or RNA.

C. Reasons for Traversal

In Applicants' view, it would not be an undue burden to search the groups. Applicants note that only two groups are recited in view of the amendment of claim 252.

It is additionally Applicants position that the groups recited are indeed not distinct. The claimed construct could comprise both DNA and RNA. Given that the construct could contain both groups, the recited groups are not mutually

exclusive and overlap in scope. Further, the claimed construct whether comprising DNA or RNA, would have a similar function, template for synthesis of a nucleic acid product having biological activity. It is Applicants' view that these groups should not have different classifications and should not require a different field of search.

VII. Whether 1) at least one nucleotide analog is modified on 1) the backbone; 2) a side chain; or 3) both (claim 255)

A. Election- Applicants elect with traverse "at least one nucleotide analog is modified on the side chain".

B. Claims readable on the Election: 255. Claim 255 has been amended to recite that "at least one nucleotide is modified at least on the backbone or side-chain"

C. Reasons for Traversal

Applicants traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 255 just recites two groups.

Claim 255 has been amended to recite "at least one nucleotide is modified at least on the backbone or side-chain". Therefore, it is possible that a construct could contain one nucleotide modified on the backbone and one nucleotide modified on the side chain. Both types of modified nucleotides would have a common function; they both serve as a point of attachment of the fusogenic protein or ligand. Given that the construct could contain both groups, the recited groups are not mutually exclusive and overlap in scope. Further, it is Applicants view that these groups should not have different classifications and should not require a different field of search. Thus the inventions are not distinct.

VIII. Whether the ligand is attached to 1) a single stranded segment; 2) a double stranded segment: 3) a single stranded construct tail; 4) a sequence complementary to a construct tail; or 5) a combination of any of the foregoing (claims 264 and 273)

A. Election-A sequence complementary to a construct tail.

B. Claims readable on Election-Claims 264 and 273. Applicants note that claim 264 has been amended to read that the ligand is attached to at least one single stranded segment; 2) at least one double stranded segment: 3) at least one single stranded construct tail or 4) at least one sequence complementary to a construct tail and has deleted "a combination of any of the foregoing".

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 264 just recites four groups.

It is Applicants' view that the inventions in these groups would not be distinct. Ligands attached to single stranded segments, double stranded segments, the tail or sequence complementary to the tail would all have similar functionalities. Further, it is Applicants view that these groups should not have different classifications and should not require a different field of search. Thus the inventions are not distinct.

IX. Whether the ligand is 1) a macromolecule; 2) a small molecule; or 3) a combination of both

A. Election-The ligand is a small molecule.

B. Claims readable on Election-Claim 265. Applicants note that claim 265 has been amended to recite that the ligand is a small molecule to advance prosecution but reserves the right to file the canceled subject matter in a subsequent continuation and/or divisional application.

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups.

X. The type of non-nucleic acid entity, which may be 1) a polypeptide; 2) a protein; 3) a saccharide; 4) a fatty acid; 5) a fatty acid ester; or 6) a combination of any of the foregoing (claim 271)

A. Election-A saccharide.

B. Claims readable on Election-Claim 271. Applicants note that claim 271 has been amended to delete "a combination of any of the foregoing".

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 271 as amended just recites four groups.

Applicants assert that the inventions in these groups would not be distinct. All of the non-nucleic acid entities recited in claim 271 confer cell targeting. Thus all of the groups have similar functionalities. Further, it is Applicants view that these groups should not have different classifications and should not require a different field of search. Thus the inventions are not distinct.

XI. Whether the non-nucleic acid entity further confers 1) cellular localization; 2) nuclear localization; or 3) a combination of any of the foregoing (claim 272)

A. Election-Nuclear localization.

B. Claims readable on Election-Claims 272, 274 and 275. Applicants note that claim 272 has been amended to delete "a combination of any of the foregoing". Claim 274 has been amended to recite and new claim 275 recites that the non-nucleic acid entity comprises a cellular localization or nuclear localization signal.

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 272 as amended just recites two groups. Furthermore, Applicants assert that the two specified groups actually do overlap. Nuclear localization could be considered to be cellular localization. Further, it is Applicants' view that these groups should not have different classifications and should not require a different field of search. Thus the inventions are not distinct.

XII. Whether the non-nucleic acid entity confers 1) nuclease resistance; 2) cell targeting; 3) cellular localization; 4) nuclear localization; or 5) a combination of any of the foregoing.

A. Election-Cellular targeting.

B.Claims readable on Election-Claim 273. Applicants note that claim 273 has been amended to delete "a combination of any of the foregoing" and delete reference to "cellular localization" and "nuclear localization". These are recited in new claim 275 where it is recited that the construct may further comprise a non-nucleic acid entity that confers cellular localization or nuclear localization.

C. Reasons for Traversal

Applicants again traverse since it would not be an undue burden to search the recited groups and the inventions are not distinct. Claim 273 as amended just recites two groups. Furthermore, in Applicants view, the recited groups are not distinct for a number of reasons. Specifically, there is overlap between the groups. A non-nucleic acid entity may confer both nuclease resistance and cell targeting which would of course occur together. Further, it is Applicants view that these groups should not have different classifications and should not require a different field of search. Thus, the inventions are not distinct.

XIII. Additional Arguments

Applicants further wish to point out that the independent claims, 246, 271 and 273 and the dependent claims 247, 248, 252, 255, 264, 272 all contain Markush groups. It is stated in MPEP 803.02:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all members of the Markush group in the clam on the merits, even though they may be directed to independent and distinct inventions.

As argued above, it is Applicants' position that the members of the Markush group are sufficiently few in number.

It is further stated in MPEP 803.02,

> In applications containing a Markush-type claim that encompasses at least two independent or distinct inventions, the examiner may require a provisional election of a single species prior to examination on the merits…Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability…

Thus, even assuming arguendo that the Restriction Requirement is proper, the election of the various groups set forth in the groups above should merely be treated as species elections.

Even assuming *arguendo* that Markush practice does not apply, Applicants assert that Linking claim practice should be in effect for Claims 271 and 273.

XIV. SUMMARY AND CONCLUSIONS

In summary and to be completely responsive, the claims readable on the elected subject matter include all of the claims currently pending: 246-252, 255, 264, 265, 266, 271-274 and 275

Furthermore, Applicants wish to again emphasize the traversal of the Restriction Requirement in its entirety. In Applicants' view, it would not be an

undue burden to search the groups enumerated. Further, many of the groups recited would not be distinct. Additionally, even assuming *arguendo* that the Restriction Requirement is proper, the election of the various groups set forth in the groups above should merely be treated as species elections **not** as an election of a single independent or distinct invention given that independent claims, 246, 271 and 273 and the dependent claims 247, 248, 252, 255, 264, 272 all contain Markush groups.

The Applicants respectfully request that this Restriction Requirement be withdrawn. The Examiner is invited to contact the undersigned if he wishes to discuss this Restriction Requirement. In the event that the Restriction Requirement is made final, Applicants reserve the right to submit a Petition to the Director to review said requirement.

Respectfully submitted,

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